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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,279	06/01/2006	James McCabe	056291-5292	6162

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
06/23/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,279	MCCABE, JAMES	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/01/07, 1/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21 are pending.

Claim Rejections - 35 USC § 103

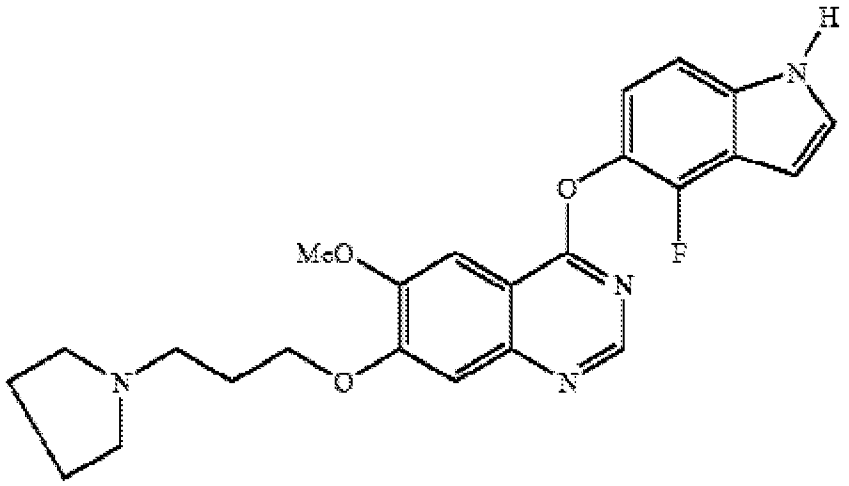
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1-16, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Stokes et. al.** (US 7,074,800 B1). In column 43, Stokes lists a compound of *4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline* which is the same as AZD2171, see the following structure:



The reference does not disclose the particular maleate salt of said compound. However, in column 49, Stokes lists several pharmaceutical salts which include the salt of maleic acid. Thus, it would have been obvious to make and use a maleate salt of AZD2171 in view of the teaching above.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 17-20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 17-20 are process claims but depend on a compound claim. Thus, it is unclear if they are independent process claims or dependent compound claims.

b. **Use Claim:** Claim 20 provides for the use of the maleate salt of AZD2171, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

c. Claim 21 recites a "method for producing an antiangiogenic and/or vascular permeability reducing effect" which does not clearly have an indication for a particular disease. Defining a disease(s) by its (their) underlying cause renders the scope of intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood. Additionally, determining whether a given disease responds or not to vascular permeability involves much experimentation since a negative response from one patient does not mean the drug isn't useful as no drug has 100% effectiveness. Thus what "success rate" determines if a particular inhibitor is effective and how many patients (and dosage regimens) need to be tested? The test for determining compliance with 35 USC 112, par.two is whether applicants have clearly defined "their" invention not what may be discovered by future research as this type of claim language clearly requires.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Use Claim: Claim 20 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112, First Paragraph

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Scope of Enablement:** Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being **enabling** for the treatment of lung cancer, does **not** reasonably provide **enable**ment for the treatment of other cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> The following factors have been considered in the determination of an enabling disclosure:
>
> (1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 21 recites a "*method for producing an antiangiogenic and/or vascular permeability reducing effect...*" The claimed method covers the treatment for all types of angiogenic diseases such as:

> angiogenesis and/or increased vascular permeability such as cancer (including leukaemia, multiple myeloma and lymphoma), diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, lymphoedema, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation including macular degeneration.

Examples of various tumors and cancers include Lymphoblastic Leukemia, Myeloid Leukemia, Adrenocortical Carcinoma, Hepatocellular Cancer, Liver Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma, Soft Tissue Sarcoma, AIDS-related Maglinancies, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Tumors, Breast Cancer, CNS Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical

Cancer, Medulloblastoma, Pancreatic Cancer, Endometrial Cancer, Ewing's Sarcoma, Gastric Cancer, Germ Cell Tumors, Gestational Trophoblastic Tumors, Hairy Cell Leukemia, Head and Neck Cancer, Intraocular Melonoma, Hypopharyngeal Cancer, Intestinal Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lung Cancer, Osteosarcoma, Skin Cancer, Retinoblastoma, Rhabdomyosarcoma, Thyoma,… etc.

Clearly, the scope of cancers alone affects many organs, and covers a huge range of disorders and complications thereof. Thus, the scope of "*antiangiogenic and/or vascular permeability*" is unduly broad.

The amount of direction or guidance presented: The claimed compound inhibits receptor tyrosine kinase. Said receptor is found in stromal endothelial cells and solid tumors which are related to breast, ovarian, colorectal, and lung cancer. The specification describes *in-vitro* bioassays using Sf21 cells (insect ovarian cells) and CaLu-6 (lung carcinoma cells). There is no data or evidence on reduction of tumor size or cell growth for other cancers that are supposedly related to the cited receptors. Thus, the specification does not provide sufficient enablement for one skilled in the art to select AZD2171 maleate salt to treat a variety of diseases related to receptor tyrosine kinase.

The state of the prior art: As evident by **Zwick et. al.** (Endocrine-Related Cancer, (2001), Vol. 8, pp. 161-173), a related compound, SU5416 (a VEGFR-2 inhibitor) is shown to be effective for treating tumours like Kaposi's sarcoma, non-small cell lung cancer, colorectal cancer and breast cancer. Thus, the state of the art does not correlate the inhibition of VEGFR to

treat all types of cancers as encompassed by the term "antiangiogenic and/or vascular permeability". Therefore, the state of the art does not support the scope of the claimed method.

The relative skill of those in the art: There has never been a compound capable of treating cancer generally, let alone treating all kinds of disorder related to receptor tyrosine kinase. Different types of cancers affect different organs and have different modes of growth and harm to the body as well as different vulnerabilities. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Therefore, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or all angiogenic disorders in general.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the showing of inhibiting receptor tyrosine kinase alone does not guarantee the compound's effectiveness in treating all cancers that are allegedly related to said kinase.

See ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Thus, given the unpredictable nature of the art, and the preliminary research in the art, one skilled in the art will have to carry out undue experimentation to practice the method of treatment recited in claim 21. When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, ***In re Ferens***, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that

achieving such a goal requires undue experimentation, ***Genetech vs. Novo Nordisk***, 42 USPQ 2nd 1001, 1006.

Information Disclosure Statement

The IDS of 11-01-07 needs to have names listed for all foreign documents (entries #19-50).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tamthom N. Truong/
Patent Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

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6-19-09